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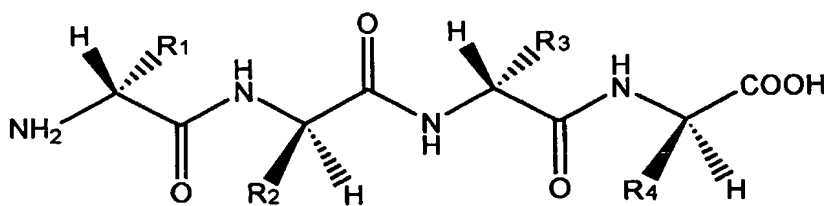
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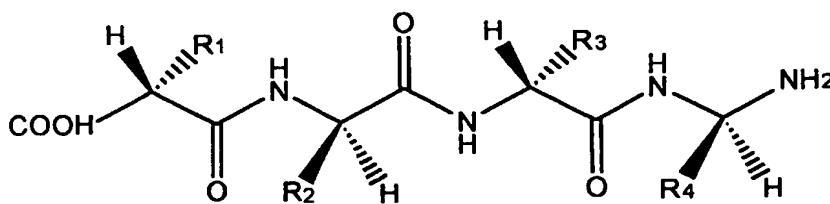
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(54) Title: A PHARMACEUTICAL COMPOSITION COMPRISING A RETRO-IVERSO ISOMER PETTIDE



I

(57) Abstract: The present invention provides a pharmaceutical composition comprising a peptide selected from the group consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val as an active component. The composition of the present invention has great efficacy in lowering serum triglyceride levels.



II

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A PHARMACEUTICAL COMPOSITION COMPRISING A RETRO-IVERSO ISOMER PEPTIDE

Technical Field

5 The present invention relates to therapeutic peptides that possess inhibitory activity towards elevation of serum triglyceride (triacylglycerol) levels, an unavoidable result that occurs upon ingestion of meals containing high composition of fat. Administration of such peptides before or concomitantly with meals allows for less net absorption of fatty
10 acids into the system, thereby contributing to the prevention of various known cardiovascular diseases as well as obesity-related ailments in general.

Background Art

15 High serum triglyceride level, independent of the well-known risk factor of serum cholesterol, has been regarded as an additional risk factor for developing cardiovascular diseases, including coronary heart disease (Austin MA, *Am. J. epidemiol.* 129: 249-59,1989) and atherosclerosis (Patsch JR et al, *Arterioscler. Thromb.* 12: 1336-45,
20 1992). A number of pharmaceutical developments have been made to restrict the elevation of serum triglyceride levels to prevent such cardiovascular ailments.

 More significantly, the excessive intake of lipid with respect to energy expenditure leads to obesity, which is currently being regarded as
25 one of the prime health concerns in the Western World. Obesity is a complex medical disorder with implications for diabetes, high cholesterol, cardiovascular conditions, some forms of cancer, and is a major cause of premature mortality. Dietary restriction and behavioral changes are key to prevent obesity, however it is now becoming evident that the success
30 in preventing or treating obesity can be increased with pharmaco-therapy. Several drugs have been developed to combat obesity, however most of

these are central-nervous system (CNS)-active, and hence have high abuse potential. Therefore, it would be desirable to have a pharmaceutical agent that would not have these dependency complications.

5 Recently, a group of low molecular weight peptides which were originally obtained and purified from a non-specific enzymatic proteolysate preparation of bovine reticulocyte protein has been shown to inhibit the elevation of serum triglyceride levels (US Patent 5,958,885). The peptides isolated are low molecular weight, i.e. 3-4 residues in
10 length, and are comprised solely of natural amino acids.

 Now, retro-inverso technology, in which oligopeptides are synthesised that are similar to naturally occurring oligo-peptides but with mirror image amino acids put in reverse sequence order (Chorev M, Goodman M, TIBTECH 13:438-45, 1995), is a technology that has had
15 limited take-up in recent years. By utilizing non-natural D-amino acids instead of L-amino acids, it can provide an advantage in bioavailability due to inherent resistance against various natural proteases *in vivo* but there is no expectation for its use to effectively mimic or better the biological action of naturally occurring peptides.

20

Disclosure of the Invention

 The present invention provides a pharmaceutical composition or a food composition for administration to a human or an animal comprising a retro-inverso isomer peptide as an active component.

25

Best mode for carrying out the Invention

 In one aspect of the present invention there is provided a pharmaceutical composition for administration to a human or an animal comprising , as an active component, a peptide selected from the group
30 consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val.

These peptides have unexpectedly been found to have a biological activity to reduce serum triglycerides. Among them, the peptides of D-Pro D-Tyr D-Val and D-Leu D-Thr D-Val substantially exceed the activity of the corresponding natural oligopeptide.

5 Unlike the natural oligopeptides, the peptides obtained from the retro-inverso chemical synthesis process are also available for functional group modifications, if required. This modification further allows for greater specificity and selectivity, and will also permit to tailor the activities of the peptides to suit the patient based on his/her intake of fat
10 composition.

The peptide may, within the scope of the claimed invention, have minor modifications of a nature that is compatible with biological systems, suitably including phosphorylation; sulphonation or iodination of the D-Tyr and / or D-Thr. The D-Pro may, for example, be hydroxylated.
15 Widely used automatic solid-phase peptide synthetic methods for performing the modification include N-alpha-acetylation or N-alpha-formylation for eliminating the positive charge of the N-terminus. When desiring to eliminate the negative charge on the C-terminus, a C-terminal carboxamide or alcohol ester can be readily generated by
20 adopting standard solid-phase peptide synthetic resins.

For optimal activity, the peptide may be modified at the N or C, and suitably both, terminals of the peptide.

Complete reversal of ionization state can also be straightforwardly performed. The N-terminal NH₂ group is suitably replaced with a COOH
25 group and the C-terminal COOH group is suitably replaced with an NH₂ group. This modification may suitably be undertaken using one of the conventional techniques for this purpose.

A route for this modification involves:

- 30 (1) a C-2 substituted malonyl (or malonamyl) residue substitution for the N-terminal retro-inverso peptide residue, and
- (2) a *gem*-diamino alkyl residue substitution for the C-terminal retro-inverso peptide residue.

The pharmaceutical composition is suitably provided in a form selected from the group consisting of a tablet, a powder, a granule, a pill and an injectable form. If provided in an injectable form it is suitably selected from the group consisting of a solution, a suspension and an emulsion.

The said injectable form may be administered by intravenous, intramuscular, subcutaneous, intracutaneous and intraperitoneal administration. The pharmaceutical composition suitably comprises from 1 to 100 mg of said peptide.

According to a second aspect of the invention there is suitably provided a food composition for administration to a human or an animal comprising a peptide consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val as an active component.

The present invention is further illustrated and described by the following examples, which should not be taken to limit the scope of the invention.

Example 1. Chemical Synthesis and Purification of Peptides

Peptides of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val and D-Leu D-Thr D-Val were synthesized on an Applied Biosystems/Perkin-Elmer 432A Synergy Peptide Synthesizer using FastMoc cycles. The synthesis chemistry involves 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) / piperidine activation, and uses dimethylformamide (DMF) / N-methylpyrrolidine (NMP) / dimethylsulfoxide (DMSO) as the coupling solvent. Synergy Fmoc-Amide resin (Applied Biosystems/Perkin-Elmer) or Rink amide methylbenzhydrylamine (MBHA) resin (NOVAbiochem) was used for the solid-phase support. The constituting N- α -9-fluorenylmethoxycarbonyl (Fmoc) protected D-amino acids (N- α -Fmoc-D-proline, N- α -Fmoc-O-t-butyl-D-tyrosine, N- α -Fmoc-D-valine, N- α -Fmoc-D-leucine, N- α -Fmoc-O-t-butyl-D-threonine) were from

NOVABIOCHEM. The peptides were cleaved by adding 1.8 ml of trifluoroacetic acid (TFA) with 0.1 ml of 1,2-ethanedithiol (EDT) and 0.1 ml of thioanisole as scavengers for 1 hour, then precipitated with 15 ml of methyl tert-butyl ether (MTBE) at 4°C and centrifugation at 2000 xg. 5 The MTBE washing was repeated three more times, and the peptides were solubilized with 20% acetic acid. To use as reference compounds, L-Val-L-Val-L-Tyr-L-Pro, L-Val-L-Tyr-L-Pro, and L-Val-L-Thr-L-Leu peptides were prepared using the same methodology.

When necessary, purification of the peptides was performed using 10 preparative reversed-phase HPLC. A Kromasil KR-100-10-C8 (10 mm x 250 mm, C8, 10 µm, 100 Å, Akzo Nobel) Column was used, with a linear gradient of 5 to 20% acetonitrile (CH₃CN) in 0.1% TFA over 20 column volumes. The fractionated peak was checked for purity using a Vydac (Registered Trade Mark) 218TP52 RP-HPLC column (2.1 mm x 15 250 mm, C8, 5 µm, 300 Å) with a linear gradient of 1 to 25% CH₃CN in 0.1% TFA. The final purity of each peptide was greater than 97%. MALDI-TOF mass spectrometry analyses using cinnapinic acid as matrix on a Kompact Research MALDI IV instrument (Kratos Analytical) confirmed the identities of the peptides.

20

Example 2. Oral Administration of Chemically Synthesised Peptides to Determine Inhibition of Triglyceride Level Elevation After Feeding

Olive oil (250 mg) was administered via gastric intubation to male 25 ICR mice (6-week old, body weight: 20 g), which were fasted overnight. The peptides were dissolved in 0.1 ml saline solution and administered orally one hour after lipid administration. For the control group, 0.1 ml of saline solution was administered per mouse. After two hours, blood was collected from the orbital vein under ether anesthesia and the serum 30 was separated by centrifugation (3000 rpm, 30 min, 1°C). Serum triglyceride levels were assayed using commercially available methods

(e.g. INFINITY (Registered Trade Mark) triglycerides reagent; Sigma Chemical Co.). The results were compared with L-Val-L-Val-L-Tyr-L-Pro (Reference Peptide 1), L-Val-L-Tyr-L-Pro (Reference Peptide 2), and L-Val-L-Thr-L-Leu (Reference Peptide 3) and shown in Table 1.

Table 1

	Peptide Dosage (mg / mouse)	Number of animal (n)	Serum Triglyceride (mg / 100 ml)	% Decrease
Distilled Water Only	-	5	92.2 ± 15.7	-
Olive Oil Only	-	24	376.2 ± 23.8	-
SEQ ID No. 1 (D-Pro D-Tyr D-Val D-Val C-NH ₂)	1.0	14	313.7 ± 45.9	22.0 %
Ref. Peptide 1 (L-Val L-Val L-Tyr L-Pro)	1.0	7	244.7 ± 25.5	46.3 %
SEQ ID No. 2 (D-Pro D-Tyr D-Val C-NH ₂)	1.0	7	231.8 ± 27.6	50.8 %
Ref. Peptide 2 (L-Val L-Tyr L-Pro)	1.0	14	407.7 ± 42.0	0 %
SEQ ID No. 3 (D-Leu D-Thr D-Val C-NH ₂)	1.0	7	294.6 ± 33.8	28.7 %
Ref. Peptide 3 (L-Val L-Thr L-Leu)	1.0	14	352.7 ± 35.6	8.3 %

In Table 1, "C-NH₂" means that the C-terminal of a peptide has a carboxamide form.

As shown in Table 1, SEQ ID NO. 2 and SEQ ID NO. 3 display higher activities in lowering elevated serum triglyceride levels than Reference 2 and 3, respectively. SEQ ID NO. 1, although less active than Reference Peptide 1, nevertheless exhibits demonstrable serum

triglyceride lowering activity, its activity being about half of Reference Peptide 1. In general, it can be shown that for the three cases, there exist at least 20 % or greater statistically significant decrease in serum triglyceride levels, and for the cases of tripeptides, the retro-inverso compounds substantially exceed the activity of the corresponding natural oligo-peptides.

As noted previously, for enhanced efficacy the retro-inverso peptides suitably have modified N and C terminals, where the N-terminal of the retro-inverso peptide is converted to replace the NH₂ group with a COOH group and the C-terminal COOH group is replaced with an NH₂ group. This modification may be achieved by carrying out a C-2 substituted malonyl (or malonamyl) residue substitution for the N-terminal retro-inverso peptide residue (Residue R₁ in Fig. 1), and a *gem*-diamino alkyl residue substitution for the C-terminal retro-inverso peptide residue (Residue R₄).

Figure 1 shows the structural differences between the retro-inverso peptide H-D-R₁-D-R₂-D-R₃-D-R₄-OH (Structure 1) and the end-group modified peptide HO-*m*R₁-D-R₂-D-R₃-*g*R₄-H (Structure II, where *m* and *g* denote malonyl and *gem*-diaminoalkyl residues, respectively).

Procedures to accomplish these end group modifications are well-documented, and are reviewed in Fletcher MD, Campbell MM, Chem Rev 1998, 98: 763-795 and Chorev M, Goodman, Acc Chem Res 1993, 26:266-73.

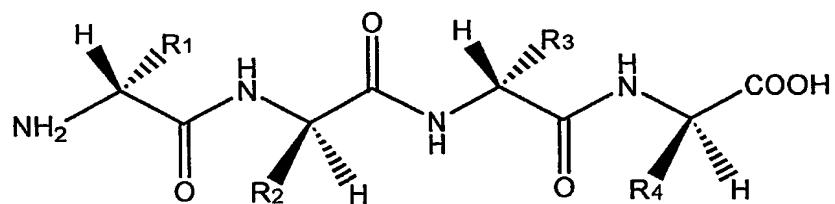
According to the present invention, it becomes possible to prevent hyperlipemia in human and domestic animals upon administration of the peptides found in the sequence listing. Such treatment is now known to have far reaching benefits, including but not restricted to, cardiovascular ailments such as hypertension and arteriosclerosis, and obesity-related complications in general.

What is claimed is:

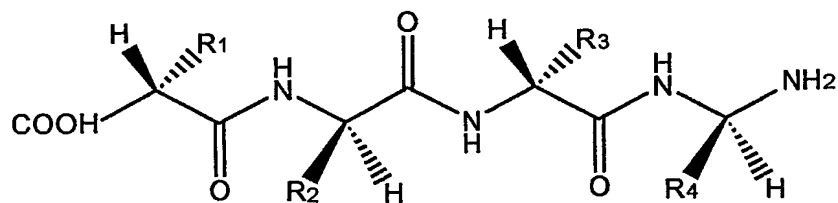
1. A pharmaceutical composition for administration to a human or an animal comprising a peptide selected from the group consisting of D-Pro D-Tyr D-Val D-Val, D-Pro D-Tyr D-Val, and D-Leu D-Thr D-Val as an active component.
5
2. The pharmaceutical composition of claim 1, being selected from the group consisting of a tablet, a powder, a granule, a pill and an injectable form.
10
3. The pharmaceutical composition of claim 2, which is an injectable form.
4. The pharmaceutical composition of claim 3, wherein said injectable form is selected from the group consisting of a solution, a suspension and a emulsion.
15
5. The pharmaceutical composition of claim 1, wherein the composition comprises from 1 to 100 mg of said peptide.
20
6. A pharmaceutical composition as claimed in any of claims 1 to 5, wherein the N-terminal NH₂ group is replaced with a COOH group and/or the C-terminal COOH group is replaced with an NH₂ group.
7. A food composition for administration to a human or an animal comprising a peptide selected from the group consisting of D-Pro D-Tyr D-Val D-Val or D-Pro D-Tyr D-Val or D-Leu D-Thr D-Val as an active component.
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FIG. 1



I



II

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER IPC7 A61K 38/04 According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC7 A61K 38/04, A61K 38/07, A23L 1/305, A23K 1/16, C07K 5/103 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Korean Patents and applications for inventions since 1975 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN, PUBMED, DELPHION, KISTI				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	WO 97/00890 A1 (ITOHAM FOODS INC.) 09 JANUARY 1997 see the whole document	1-7		
Y	EP 0838473 A1 (HANKYU KYOEI BUSSAN CO., LTD.) 29 APRIL 1998 see the page1 line5 - page5 line3 page7 line34 - page8 line54 page1 line5 - page5 line3 all claims	1-7		
Y	WO 8906970 A1 (HANKYU KYOEI BUSSAN CO., LTD.) 10 AUGUST 1989 see the whole document	1-7		
A	US 5756467 (HANKYU KYOEI BUSSAN CO., LTD.) 26 MAY 1998 see the whole document	1-7		
A	JP 11263733 A2 (HANKYU KYOEI BUSSAN CO., LTD.) 28 SEPTEMBER 1999	1-7		
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.				
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Date of the actual completion of the international search 26 AUGUST 2003 (26.08.2003)		Date of mailing of the international search report 27 AUGUST 2003 (27.08.2003)		
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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IPC7 A61K 38/04

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Minimum documentation searched (classification system followed by classification symbols)

IPC7 A61K 38/04, A61K 38/07, A23L 1/305, A23K 1/16, C07K 5/103

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26 AUGUST 2003 (26.08.2003)

Date of mailing of the international search report

27 AUGUST 2003 (27.08.2003)

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CHO, Hee Won

Telephone No. 82-42-481-5607



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Information on patent family members

International application No.

PCT/KR03/01017

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